

hydroxypethidine, ibufenac, p-lactophenetide, levorphanol, meptazinol, metazocine, metopon, morphine, nalbuphine, nico-morphine, norlevorphanol, normorphine, oxycodone, oxymorphone, pentazocine, phenazocine, phenocoll, phenoperidine, phenyl-butazone, phenylsalicylate, phenylramidol, salicin, salicyl-amide, tiorphan, tramadol, diacerein, actarit; paracetamol is not a cox-inhibitor;

for respiratory and urogenital apparatus drugs (bronchodilators and drugs active on the cholinergic system, expectorants/mucolytics, antiasthmatic/antiallergic antihistaminic drugs), the following can be mentioned:

bronchodilators and drugs active on the cholinergic system: acefyline, albuterol, bambuterol, bamiphylline, bevonium methyl sulphate, bitolterol, carbuterol, clenbuterol, chlorprenaline, dioxethedrine, difylline, ephedrine, epinephrine, eprozinol, etafredine, ethylnorepinephrine, etofylline, fenoterol, flutoprium bromide, hexoprenaline, ipratropium bromide, isoetharine, isoproterenol, mabuterol, metaproterenol, oxybutynin, oxitropium bromide, pirbuterol, procaterol, protokylol, proxyphylline, reproterol, rimiterol, salmeterol, soterenol, terbutaline, 1-teobromineacetic acid, tiotropium bromide, tretoquinol, tulobuterol, zaprinast, cyclodrine, NS-21, 2-hydroxy-2,2-diphenyl-N-(1,2,3,6-tetra hydro-pyridin-4-ylmethyl)acetamide;

expectorant/mucolytic drugs: acetyl-cysteine, ambroxol, bromhexine, carbocysteine, domiodol, erdosteine, ferulic acid, guaiacol, guaifenesin, iodinated glycerol, letosteine, mecysteine hydrochloride, mesna, sobrerol, stepronin, terpin, tiopronin;

antiasthmatic/antiallergic antihistaminic drugs: acrivastine, alloclamide, amlexanox, cetirizine, clobenzepam, chromoglycate, chromolyn, epinastine, fexofenadine, formoterol, histamine, hydroxyzine, levocabastine, lodoxamide, mabuterol, metron S, montelukast, nedocromil, repirinast, seratrodast, suplatast tosylate, terfenadine, tiaramide, urushiol, bromhexine;

for cardiovascular drugs (ACE-inhibitors, beta-blockers, antithrombotic and vasodilator drugs, antidiabetic and hypoglycemic drugs), the following can be mentioned:

ACE-inhibitors: alacepril, benazepril, captopril, cero-napril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, imidapril, lisinopril, losartan, moxeltipril, naphthopidil, perindopril, quinapril, ramipril, spirapril, temocapril, trandolapril, urapidil;

beta-blockers: acebutolol, alprenolol, amosulalol, arotinolol, atenolol, betaxolol, bevantolol, bucumolol, bufetolol, bufuralol, bunitrolol, bupranolol, butofadol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, dilevalol, epanolol, esmolol, indenolol, labetalol, mepindolol, metipranolol, metoprolol, moperolol, nadolol, nadoxolol, nebivolol, nifenalol, nipridalol, oxprenolol, penbutolol, pindolol, practolol, pronethalol, propranolol, sotalol, sulfinalol, talinolol, tertatolol, tilisolol, timolol, toliprolol, xibenolol;

antithrombotic and vasoactive drugs: acitorphan, acetylsalicylic acid, argatroban, bamethan, benfurodil hemisuccinate, benziodarone, betahistine, brovincamine, bufeniode, citicoline, clobenfurol, clopidogrel, cyclandelate, dalteparin, dipyridamole, droprenilamine, enoxaparin, fendifline, ifenprodil, iloprost, indobufen, isbogrel, isoxsuprine, heparin, lamifiban, midrodine, nadroparin, nicotinyl alcohol, nyldrin, ozagrel, perhexiline, phenylpropanolamine, prenylamine, papaveroline, reviparin salt, ridogrel, suloctidil, tinofedrine, tinzaparin, trifusal, xanthinol niacinate;

antidiabetic drugs: acarbose, carbutamide, glibornuride glybuthiazol(e), miglitol, repaglinide, troglitazone, 1-butyl-3-metanyl-urea, tolrestat, nicotinamide;

for antitumoral drugs, the following can be mentioned: ancitabine, anthramycin, azacitidine, azaserine, 6-azauridine, bicalutamide, carubicin, carzinophilin, chlorambucil, chlorozotocin, cytarabine, daunorubicin, defosfamide, demeclocine, denopterin, 6-diazo-5-oxo-L-norleucine, docetaxel, doxifluridine, doxorubicin, droloxifene, edatrexate, eflornithine, enocitabine, epirubicin, epitiostanol, etanidazole, etoposide, fenretinide, fludarabine, fluorouracil, gemcitabine, hexestrol, idarubicin, lonidamine, mannomustine, melphalan, menogaril, 6-mercaptopurine, methotrexate, mitobronitol, mitolactol, mitomycins, mitoxantrone, moperidol, mycophenolic acid, ninopterin, nogalamycin, paclitaxel, pentostatin, pira-

rubicin, piritrexim, plicamycin, podophyllic acid, porfimer sodium, porfiromycin, propagermanium, puromycin, ranimustine, retinoic acid, roquinimex, streptonigrin, streptozocin, teniposide, tenuazonic acid, thiamiprine, thioguanine, tomudex, topotecan, trimetrexate, tubercidin, ubenimex, vinblastine, vincristine, vindesine, vinorelbine, zorubicin;

for antiulcer drugs the following can be mentioned: acetamidocaproic acid, arbaprostil, cetraxate, cimetidine, ecabet, enprostil, esaprazole, irsogladine, misoprostol, omeprazole, ornoprostil, pantoprazole, plaunotol, rioprostil, rosaproston, rotraxate, sofalcone, trimoprostil;

among anti-hyperlipidemic drugs (statines) the following can be mentioned: atorvastatin, cilastatin, dermostatin, fluvastatin, lovastatin, mevastatin, nystatin, pentostatin, pepstatin, pravastatin sodium, simvastatin;

among antibiotic/antiviral drugs the following can be mentioned:

antibiotics: amdinocillin, amoxicillin, ampicillin, apalcillin, apicycline, aspoxicillin, azidamfenicol, azidocillin, azlocillin, aztreonam, benzoylpas, benzyl penicillinic acid, biapenem, bicozamycin, capreomycin, carbenicillin, carindacillin, carumonam, cefaclor, cefadroxil, cefamandole, cefatrizine, cefazedone, cefazolin, cefbuperazone, cefclidin, cefdinir, cefditoren, cefepime, cefetamet, cefixime, cefmenoxime, cefmetazole, cefminox, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotetan, cefotiam, cefoxitin, cefozopran, cefpimizole, cefpiramide, cefpirome, cefprozil, cefroxadine, cefsulodin, ceftazidime, cefteram, ceftezole, ceftibuten, ceftiofur, ceftizoxime, ceftriaxone, cefuroxime, cefuzonam, cephacetrile sodium, cephalexin, cephaloglycin, cephaloridine, cephalosporin C, cephalothin, cephapirin sodium, cephadrine, chloramphenicol, chlortetracycline, cinoxacin, clavulanic acid, clometocillin, cloxacillin, cyclacillin, cycloserine, demeclocycline, dicloxacillin, epicillin, fenbeccillin, flomoxef, floxacillin, hetacillie, imipenem, lenampicillin, loracarbef, lymecycline, mafenide, mecloxycline, meropenem, metampicillin, methacycline, methicillin sodium, mezlocillin, minocycline, moxalactam, mupirocin, myxin, negamycin, novobiocin, oxacillin, panipenem, penicillin G potassium salt,

penicillin N, penicillin O, penicillin V, phenethicillin potassium salt, pipacycline, piperacillin, pirlimycin, porfomycine, propicillin, quinacillin, ritipenem, rolitetraacycline, sancycline, sedecamycin, spectinomycin, sulbactam, sulfenicillin, temocillin, tetracycline, ticarcillin, tigemonam, tubercidin, azithromycin, clarithromycin, dirithromycin, enviomycin, erythromycin, josamycin, midecamycin, miokamycin, oleandomycin, rifabutin, rifamide, rifamycin, rifaximin, rokitamycin, spiramycin, troleandomycin, viomycin, virginiamycin;

amikacin, apramycin, arbekacin, dibekacin, dihydrostreptomycin, fortimicins, gentamicin, micronomicin, neomycin, netilmicin, paromomycin, ribostamycin, sisomicin, spectinomycin, streptomicin, tobramycin, trospectomycin;

bacampicillin, cefcapene pivoxil, cefpodoxime proxetil, panipenem, pivampicillin, pivcefalexin, sultamicillin, talampicillin;

carbomycin, clindamycin, lincomycin, mikamycin, rosaramycin, ciprofloxacin, clinafloxacin, difloxacin, enoxacin, enrofloxacin, fleroxacin, flumequine, grepafloxacin, lomefloxacin, nadifloxacin, nalidixic acid, norfloxacin, ofloxacin, pazufloxacin, pefloxacin, pipemidic acid, piromidic acid, rufloxacin, sparfloxacin, tosufloxacin, trovafloxacin, clomocycline, guamecycline, oxytetracycline, nifurpirinol, nifurprazine; p-aminosalicylic acid, p-aminosalicylic acid hydrazide, clofazimine, deoxydihydrostreptomycin, ethambutol, glyconiazide, isoniazid, opiniazide, phenyl aminosalicylate, rifampin, rifapentine, salinazid, 4-4'-sulfynyldianiline, Acediasulfone, dapsone, succisulfone, p-sulfanilylbenzylamine, thiazolsulfone, acetyl sulfamethoxypyrazine, mafenide, 4'-(methylsulfamoyl)sulfanilanilide, salazosulfadimidine, sulfabenzamide, sulfacetamide, sulfachlorpyridazine, sulfachrysoidine, sulfacytine, sulfadiazine, sulfadicramide, sulfadimethoxine, sulfadoxine, sulfathidole, sulfaguanidine, sulfaguanole, sulfalene, sulfamerazine, sulfameter, sulfamethazine, sulfamethizole, sulfamethomidine, sulfamethoxazole, sulfamethoxypyridazine, sulfamethylthiazole, sulfametrole, sulfamidochrysoidine, sulfamoxole, sulfanilamide, 2-p-sulfanilylanilinoethanol, N⁴-sulfanilylsulfanilamide,

sulfanilylurea, N-sulfanilyl-3,4-xylamide, sulfaperine, sulfaphenazole, sulfaproxyline, sulfapyrazine, sulfapyridine, sulfasomizole, sulfasymazine, sulfathiazole, sulfathiourea, sulfisomidine, sulfisoxazole, 4-sulfanilamido salicylic acid; negamycin, carumonan, cloxyquin, nitroxoline, arginine, metronidazole;

antiviral drugs: acyclovir, amantadine, cidofovir, cytarabine, didanosine, dideoxyadenosine, edoxudine, famciclovir, floxuridine, ganciclovir, idoxuridine, indanavir, kethoxal, lamivudine, MADU, penciclovir, podophyllotoxin, ribavirin, rimantadine, saquinavir, sorivudine, stavudine, trifluridine, valacyclovir, vidarabine, xenazoic acid, zalcitabine, zidovudine;

among the bone resorption inhibitors (diphosphonates) the following can be mentioned: alendronic acid, butedronic acid, etidronic acid, oxidronic acid, pamidronic acid, risedronic acid;

among antidementia drugs the following can be mentioned: amiridine, lazabemide, mofegiline, salbeluzol, oxiracetam, ipidacrine, nebracetam, tacrine, velnacrine.

The preferred substances are the following:

among anti-inflammatories: acetylsalicylic acid, 5-aminoacetylsalicylic acid, carprofen, diclofenac sodium, diflunisal, etodolac, flufenamic acid, flunixin, flurbiprofen, ibuprofen, indomethacin, indoprofen, ketoprofen, ketorolac, lornoxicam, loxoprofen, meclofenamic acid, mefenamic acid, meloxicam, mesalamine, naproxen, niflumic acid, olsalazine, piroxicam, salsalate, sulindac, suprofen, tenoxicam, tiaprofenic acid, tolfenamic acid, tolmetin, zomepirac, tomoxi-prol;

among analgesic drugs: acetaminophen, acetylsalicylsalicylic acid, benoxaprofen, buprenorphine, butorphanol, capsaicin, diacereine, dihydrocodeine, ethylmorphine, eugenol, phenylbutazone, meptazinol, morphine, nalbuphine, pentazocine, thiorphan, tramadol, actarit;

among respiratory and urogenital apparatus drugs: (bronchodilators; drugs active on the cholinergic system, expectorants/mucolytics, antiasthmatics/antiallergic antihistaminic drugs):

bronchodilators and drugs active on the cholinergic system: albuterol, carbuterol, clenbuterol, diphylline, etophylline, fenoterol, ipratropium bromide, metaproterenol, oxybutynin, pirbuterol, salmeterol, terbutaline, tiotropium bromide, zarinast, cyclodrine, NS-21, 2-hydroxy-2,2-diphenyl-N-(1,2,3,6-tetrahydro-pyridin-4-ylmethyl)acetamide;

expectorant/mucolytic drugs: acetyl-cysteine, ambroxol, bromexine, carbocysteine, guaiacol, ferulic acid, mecysteine hydrochloride, sofrerol;

antiasthmatic/antiallergic antihistaminic drugs: cetirizine, chromoglycate, histamine, levocabastine, lodoxamide, montelukast, terfenadine, bromhexine.

Among cardiovascular drugs:

ACE-inhibitors: captopril, enalapril, lisinopril, losartan, ramipril;

beta blockers: alprenolol, atenolol, bupranolol, labetalol, metipranolol, metoprolol, pindolol, propranolol, timolol;

antithrombotic and vasoactive drugs: acetylsalicylic acid, acitorphan, argatroban, clopidogrel, dalteparin, dipyridamole, enoxaparin, heparin, iloprost, midodrine, ozagrel, phenylpropanolamine trifusal;

antidiabetic drugs: tolrestat, nicotinamide;

among antitumoral drugs: anthramycin, daunorubicin, doxorubicin, epirubicin, fluorouracil, methotrexate, vinblastine;

among antiulcer drugs: cimetidine, omeprazole, pantoprazole;

among antihyperlipidemic drugs: lovastatin, pravastatin sodium, simvastatin;

Among antibiotic/antiviral drugs:

antibiotic drugs: amoxicillin, ampicillin, aztreonam, biapenem, carbencillin, cefaclor, cefadroxil, cefamandole, cefatrizine, cefoxitin, clavulanic acid, dicloxacillin, imipenem, mecloxycline, methacycline, moxalactam, panipenem, sulbactam, azithromycin, erythromycin, josamycin, miokamycin, rifabutine, rifamide, rifamycin, gentamicin, paromomycin, sisomicin, bacampicillin, carbomycin, clindamycin, ciprofloxacin, clinafloxacin, difloxacin, enrofloxacin, lomefloxacin, nadifloxacin, norfloxacin, ofloxacin, pipemidic

acid,

apicycline, clomocycline, oxytetracycline, nifurpirinol, nifurprazine, isoniazid, rifampin, rifapentine, dapsone, thiazolsulfone, sulfamethoxazole, sulfamoxole, metronidazole, arginine;

antiviral drugs: acyclovir, famciclovir, ganciclovir, penciclovir, ribavirin, vidarabine, zidovudine;

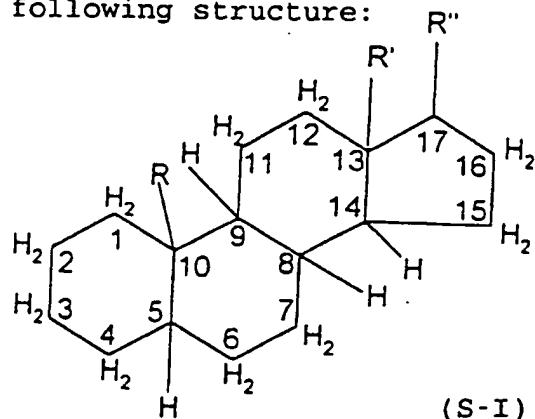
among the bone resorption inhibitors: alendronic acid, etidronic acid, pamidronic acid;

among antidementia drugs: oxiracetam, tacrine, velnacrine.

The above mentioned substances, R precursors, are prepared according to the methods known in the prior art. See for example in "The Merck Index, 12a Ed. (1996), herein incorporated by reference. When available, the corresponding isomers, comprising optical isomers, can be used.

Tomoxiprol is obtained according to the method described in EP 12,866.

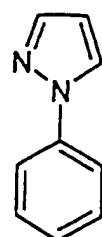
When in the compounds of formula (I) the precursor drug is a steroid, A = R- having the following structure:



wherein in substitution of the hydrogens of the CH groups or of the two hydrogens of the CH₂ groups mentioned in the general formula, the following substituents can be present:

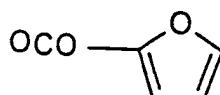
in position 1-2: there may be a double bond;

in position 2-3: there may be the following substituent:



(S-II)

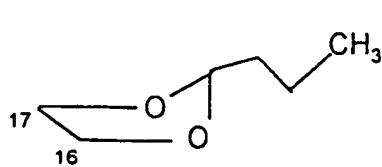
in position 2: there may be Cl, Br;
 in position 3: there may be CO, -O-CH₂-CH₂-Cl, OH;
 in position 3-4: there may be a double bond;
 in position 4-5: there may be a double bond;
 in position 5-6: there may be a double bond;
 in position 5-10: there may be a double bond;
 in position 6: there may be Cl, F, CH₃, -CHO;
 in position 7: there may be Cl, OH;
 in position 9: there may be Cl, F;
 in position 11: there may be OH, CO, Cl, CH₃;
 in position 16: there may be CH₃, OH, =CH₂:
 in position 17: there may be OH, CH₃, OCO(O)_{ua}(CH₂)_{va}CH₃, C≡CH
 or



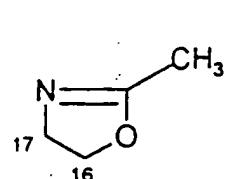
(S-III)

wherein ua is an integer equal to 0 or 1, va is an integer from 0 to 4;

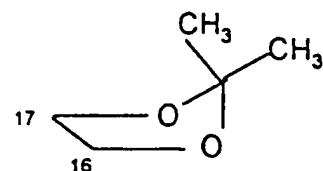
in position 16-17: there may be the following groups:



(S-IVa)



(S-IVb)



(S-IVc)

R and R', equal to or different from each other, can be hydrogen or linear or branched alkyls from 1 to 4 carbon atoms, preferably R = R' = CH₃;

R'' is -(CO-L)_t-(L)_{t2}-(X_O^I)_{t1}-

wherein t, t1 and t2 are integers equal to or different from each other, equal to 0 or 1, with the proviso that when t = 0 t2 = 1 and when t = 1 t2 = 0, and that t and t1, or t2 and t1, cannot contemporaneously be equal to 0 when A does not contain -OH groups;

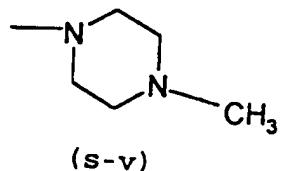
the bivalent bridging group L is selected from:

(CR₄R₅)_{na}(O)_{nb}(CR₄R₅)_{n'a}(CO)_{n'b}(O)_{n''b}(CO)_{n'''b}(CR₄R₅)_{n''a}

wherein na, n'a, and n''a, equal to or different from each other, are integers from 0 to 6, preferably 1-3; nb, n'b, n'''b

and $n'''b$, equal to or different from each other, are integers equal to 0 or 1; R_4 , R_5 , equal to or different from each other, are selected from H, linear or branched alkyl from 1 to 5 carbon atoms, preferably from 1 to 3;

X_0^I is X as above defined, or equal to X_2^I wherein X_2^I is equal to OH, CH₃, Cl, N(-CH₂-CH₃)₂, SCH₂F, SH, or



Preferably R" in the formula (S-I) is -CO-CH₂OH, or CH(CH₃)-CH₂-CH₂-COOH.

In the precursor steroids those having the hydroxyl function in position 3 and/or in position 11, and/or having in R" an hydroxyl or carboxylic function in terminal position, are preferred.

The precursor steroids of A which can be mentioned and which are preferred, are those listed hereinunder, obtainable according to the processes known in the prior art.

As precursors and respective processes, those for example described in The Merck Index, ed. 12 of 1996, herein incorporated by reference, can be mentioned. The precursors (according to the Merck nomenclature) are the following, wherein H₂, H, R, R', R'' have the meaning mentioned in the compounds listed herein: Budesonide, Hydrocortisone, Alclometasone, Algestone, Beclomethasone, Betamethasone, Chloroprednisone, Clobetasol, Clobetasone, Clocortolone, Cloprednol, Cortisone, Corticosterone, Deflazacort, Desonide, Desoximethasone, Dexamethasone, Diflorasone Diflucortolone, Difluprednate, Fluazacort, Flucinolone, Flumethasone, Flunisolide, Fluocinolone Acetonide, Fluocinonide, Fluocortyn Butyl, Fluocortolone, Fluorometholone, Fluperolone Acetate, Fluprednidene Acetate, Fluprednisolone, Flurandrenolide, Formocortal, Halcinonide, Halobetasol Propionate, Halomethasone, Halopredone Acetate, Hydrocortamate, Loteprednol Etabonate, Medrysone, Meprednisone, Methylprednisolone, Momethasone Furoate, Paramethasone, Prednicarbate, Prednisolone, Prednisolone 25-Diethylaminoacetate, Prednisolone Sodium Phosphate, Prednisone, Prednival, Prednylidene, Rimexolone, Triamcinolone, Tri-

amcinolone Acetonide, 21-Acetoxypregnenolone, Cortivazol, Amcinonide, Fluticasone Propionate, Mazipredone, Tixocortol, Triamcinolone Hexacetonide, Ursodesoxycholic acid, Chenodeoxycholic acid, Mitrienediol, Moxestrol, Ethynylestradiol, Estradiol, Mestranol.

The efficacy of the compounds according to the present invention as drugs to be used in the conditions of moderate oxidative stress has been shown also in a pharmacological test in which said compounds have been able to inhibit the cytolesive effects induced by hydrogen peroxide on human endothelial cells of the umbilical vein. The endothelial cell is one of the first cell hit in pathological processes ("Pathophysiology: the biological basis for disease in adults and children" by McCance & Huether, 1998, page 1025) and the hydrogen peroxide is a mild oxidant and is considered as an essential mediator agent in pathologies connected to oxidative stress (B. Halliwell, J. Gutteridge "Free Radicals in Biology and Medicine", page 416, 1993). The effectiveness to neutralize their cytolesive effects is considered essential for the pharmacological activity of compounds to be used under oxidative stress conditions (B. Halliwell, J. Gutteridge "Free Radicals in Biology and Medicine", page 416, 1993).

The compounds of formula (I) are prepared by means of the reactions specified below.

If the reactive function of the drug (for example -COOH, -OH) is involved in a covalent bond, for example of ester, amide, ether type, said function, before carrying out the preparation of the mentioned compounds, can be restored with the methods well known in the prior art.

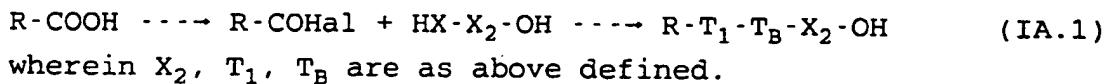
The reactions used for obtaining the compounds of formula (I) are reactions leading to the formation of bonds for example of ester, amide, thioester type well known to the skilled in the field.

When in the two reaction compounds other functional groups COOH and/or HX, wherein X is as above defined, are present, they must be protected before the reaction according to the methods known in the prior art; for example as described in the publication by Th. W. Greene: "Protective groups in organic synthesis", Harward University Press, 1980.

The compounds of formula I wherein s = 2 are prepared as mentioned hereinafter.

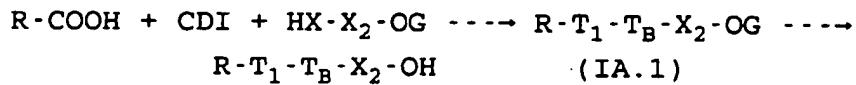
IA)- The drug has general formula R-COOH and the functional group of the precursor compound of B which links itself to the drug carboxylic function has formula XZ, X being as above defined and Z = H, an OH function or an halogen atom being also contemporaneously present in the precursor compound of B as reactive groups for the nitration reaction.

The general synthesis scheme, if in the precursor compound of B also an OH function is present, implies the initial formation of the R-COHal acid halide (Hal = Cl, Br) and the subsequent reaction with the HX group of the precursor compound of B:



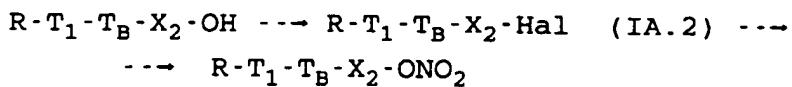
The RCOHal acylhalide is prepared according to the methods known in the prior art, for example by thionyl or oxalyl chloride, or by P^{III} or P^V halides in inert solvents under the reaction conditions, such as for example toluene, chloroform, DMF, etc. Then the acyl halide is reacted with the group HX of the precursor of B by using an inert solvent under the reaction conditions such as toluene, tetrahydrofuran, chloroform, etc. at a temperature in the range 0°C-25°C.

Alternatively to the previous synthesis, the precursor drug of formula R-COOH can be treated with an agent activating the carboxyl group selected from N,N'-carbonyldiimidazol (CDI), N,N'-dicyclohexylcarbodiimide in an inert solvent under the reaction conditions such as toluene, tetrahydrofuran, chloroform, etc. at a temperature in the range -5°C and +50°C. The obtained compound is reacted in situ with the precursor of B, after the OH function present in the precursor of B has been protected, for example by formation of an acetyl group, recovering the initial function at the end of the synthesis by the methods well known in the prior art. The reaction scheme is the following:



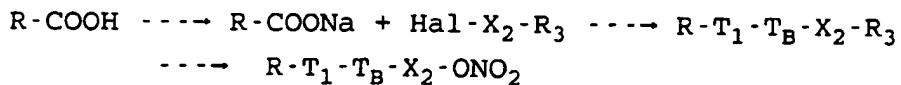
wherein X_2 , T_1 , T_B are as above defined and G is a protective group of the OH function.

The compound of formula (IA.1) is then subjected to halogenation reaction, for example by PBr_3 , PCl_5 , $SOCl_2$, PPh_3 and I_2 in an inert solvent under the reaction conditions such as toluene, tetrahydrofuran, chloroform, etc. at a temperature in the range $-5^{\circ}C$ and $+50^{\circ}C$. The halogen derivative is reacted with $AgNO_3$ in organic solvent such as acetonitrile, tetrahydrofuran at a temperature in the range $25^{\circ}C-80^{\circ}C$. The reaction scheme is the following:



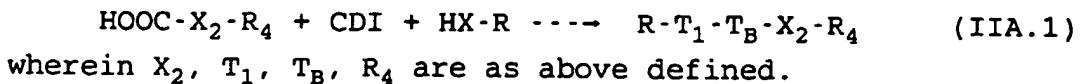
Alternatively, when X_2 is a linear C_4 alkyl, the $R-COOH$ acid is reacted with triphenylphosphine in the presence of an halogenating agent such as CBr_4 or N -bromosuccinimide in tetrahydrofuran and the resulting compound (IA.2), wherein X_2 is butylene, is nitrated as above mentioned.

Or it is possible to convert the R-COOH acid into its sodic salt, by using methods known in the prior art, and reacting it with an halogen derivative of formula Hal-X₂-R₃ wherein R₃ is OH, Hal in an inert solvent under the reaction conditions such as tetrahydrofuran, chloroform, etc. at a temperature in the range -5°C and +25°C. If R₃=Hal the obtained derivative is nitrated as above mentioned. The reaction scheme is the following:



IIA) - The drug has general formula R-XH and the functional group of the precursor compound of B which links itself to the function HX of the drug is a carboxylic group, X being as above defined, an OH function or an halogen atom being also contemporaneously present in the precursor compound of B as reactive groups for the nitration reaction.

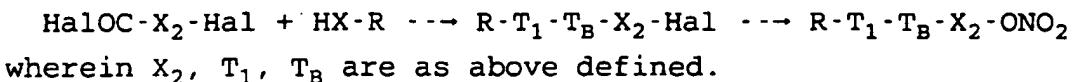
The general synthesis scheme implies the reaction of the acid HOOC-X₂-R₄ wherein R₄ is Hal, OG wherein G is a suitable protecting group, with an activating agent as mentioned in IA) and the subsequent reaction with the HX group of the drug.



The obtained compound (IIA.1) is transformed into the corresponding nitroderivative as mentioned in IA). If the

substituent OG is present, the protecting group is first removed by the known methods.

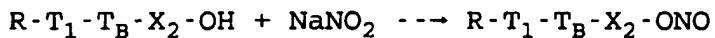
Alternatively to the previous synthesis, the drug R-OH is reacted with an acyl halide having formula Hal-X₂-COHal according to the conditions mentioned in IA) and the obtained halogen derivative is then nitrated as above mentioned:



The compounds of formula I wherein s = 1 are prepared as mentioned hereinafter.

IB) - The drug has general formula R-COOH and the functional group of the precursor compound of B which links itself to the drug carboxylic function has formula XZ, X being as above defined and Z = H, the precursor compound of B containing also an hydroxyl function or an halogen atom as reactive groups for the nitration reaction.

The compound of formula R-T₁-T_B-X₂-OH (IA.1) obtained as reported in IA) is transformed into nitroso derivative by reaction with sodium nitrite in water in the presence of hydrochloric acid, according to the procedures known in the prior art.



IIB) - The drug has general formula R-XH and the functional group of the precursor compound of B which links itself to the function HX of the drug is a carboxylic group, X being as above defined. The synthesis scheme is similar to that described in IIA).

The compound of formula R-T₁-T_B-X₂-R₄ (IIA.1), obtained as reported in IIA) is transformed into the nitroso derivative as mentioned in IB).

The compounds of the present invention are formulated in the corresponding pharmaceutical compositions for parenteral, oral and topic use according to the methods well known in the prior art, together with the usual excipients; see for example the publication "Remington's Pharmaceutical Sciences 15a Ed."

The amount on molar basis of the active principle in these formulations is the same, or lower, in comparison with that used of the corresponding precursor drug.

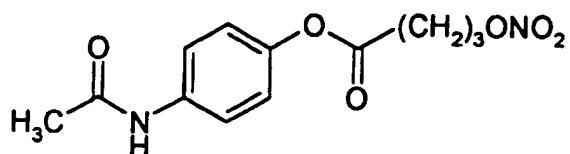
The daily administrable doses are those of precursor

drugs, or in the case lower. The daily doses can be found in the publications of the field, such as for example in "Physician's Desk reference".

The following examples have the purpose to illustrate the invention and are not to be considered as limitative of the same.

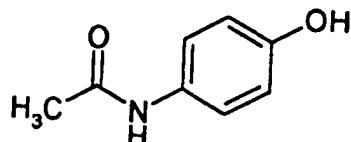
EXAMPLE 1

Preparation of 4-nitroxybutyric acid 4'-acetyl amino phenyl ester



(E-1)

The drug is paracetamol of formula



(E-1a)

The precursor compound of B is the 4-hydroxybutyric acid.

a) Preparation of 4-bromobutyric acid 4'-acetyl amino phenyl ester

To a solution of 4-bromobutyric acid (4.6 g, 27.6 mmoles) in chloroform (45 ml) and N,N-dimethylformamide (20 ml), paracetamol (4.17 g, 27.6 mmoles), N,N'-dicyclohexyl carbodiimide (8.42 g, 40.8 mmoles) and 4-dimethyl aminopyridine (0.15 g, 1.25 mmoles) are added. The reaction mixture is maintained under stirring at room temperature for 72 hours, filtered and evaporated under vacuum. The reaction crude material is treated with ethyl acetate and washed with brine and then with water. The organic phase is anhydified with sodium sulphate and then evaporated under vacuum.

The residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 4/6 (ratio V/V). 5.33 g of the

product are obtained as a white solid. M.p. = 108° - 110°C.

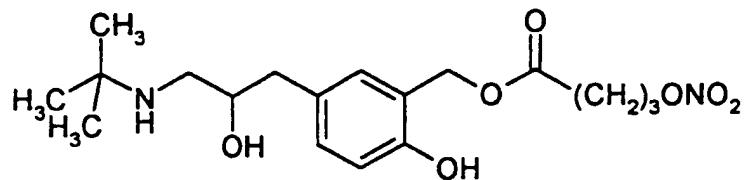
b) Preparation of 4-nitroxybutyric acid 4'-acetyl amino phenylester

To a solution of 4-bromobutyric acid 4'-acetyl amino phenyl ester (5.33 g, 17.8 mmoles) in acetonitrile (80 ml) silver nitrate (4.56 g, 26.9 mmoles) is added. The reaction mixture is heated for 16 hours away from light at 80°C, then cooled to room temperature, filtered to remove the silver salts, and evaporated under reduced pressure. The residue is purged by chromatography on silica gel eluting with n-hexane/ethyl acetate 4/6. 4.1 g of the product are obtained as a white solid. M.P.= 80-83°C.

Elementary analysis:	C	H	N
Calculated	51.07%	4.99%	9.92%
Found	51.06%	5.00%	9.90%

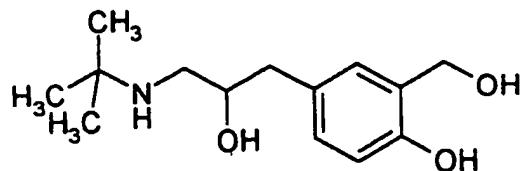
EXAMPLE 2

Preparation of 4-hydroxy-3-(4-nitroxybutanoyloxymethyl)- α -[(tertbutylamino)methyl]benzyl alcohol



(E-2)

The precursor drug is salbutamol of formula



(E-2a)

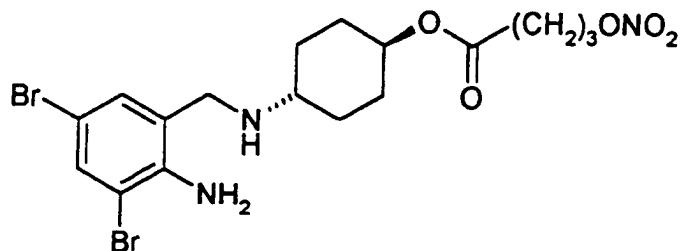
The precursor compound of B is the 4-hydroxybutyric acid.

The compound (E-2) is synthetized according to the procedure described in Example 1. Yield: 21%.

Elementary analysis:	C	H	N
Calculated	55.13%	7.07%	7.56%
Found	55.10%	7.09%	7.57%.

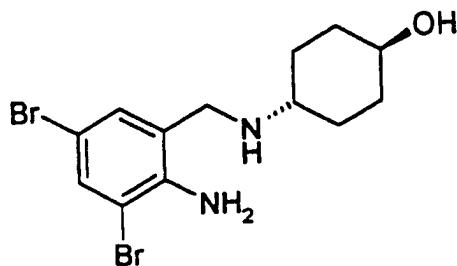
EXAMPLE 3

Preparation of 4-(nitroxy)butyric acid 4-[(2-amino-3,5-dibromophenyl)methylamino] trans cyclohexyl ester



(E-3)

The precursor drug is ambroxol



(E-3a)

The precursor compound of A is the 4-hydroxybutyric acid.

a) Preparation of 4-[(2-tert-butoxycarbonylamino-3,5-dibromophenyl)methylamino] trans cyclohexanol

To a solution of ambroxol (5 g, 13.22 mmoles) in dioxane (35 ml) and water (50 ml), triethylamine (3.31 ml, 23.7 mmoles) and di-tert-butyl dicarbonate (3.46 g, 15.86 mmoles) are added. The reaction mixture is left under stirring at room temperature for 24 hours, then concentrated at reduced pressure. The residue is treated by adding portions of a 1% HCl solution until pH 7, then the solution is extracted with ethyl acetate. The organic phase anhydified with sodium sulphate is evaporated under vacuum. 4-[(2-tert-butoxycarbonylamino-3,5-dibromophenyl)methylamino] trans cyclohexanol is obtained, which is used in the subsequent step without further

purification.

b) Preparation of 4-(nitroxy)butyric acid 4-[(2-tert-butoxycarbonylamino-3,5-dibromophenyl) methylamino] trans cyclohexyl ester

The compound is synthetized according to the procedure described in Example 1. Yield 57%.

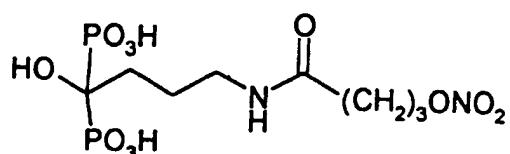
c) Preparation of 4-(nitroxy)butyric acid 4-[(2-amino-3,5-dibromophenyl) methylamino] trans cyclohexyl ester

To a solution of 4-(nitroxy)butyric acid 4-[(2-tert-butoxycarbonylamino-3,5-dibromophenyl) methylamino] trans cyclohexyl ester (3.5 g, 5.74 mmoles) in ethyl acetate (100 ml), cooled at 0°C, a 5N HCl solution in ethyl acetate (5.95 ml) is added. The solution is maintained under stirring at 0°C for 5 hours, then filtered. The obtained solid is suspended in ethyl acetate and the organic layer washed with a 5% sodium carbonate solution. The organic phase is washed with water, anhydified with sodium sulphate and evaporated at reduced pressure. The residue is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 1/1 (ratio by volume). 4-(nitroxy)butyric acid 4-[(2-amino-3,5-dibromophenyl) methylamino] trans cyclohexyl ester is obtained. Yield 31%.

	C	H	N	Br
Calculated	40.10%	4.55%	8.25%	31.38
Found	40.07%	4.54%	8.26%	31.39%

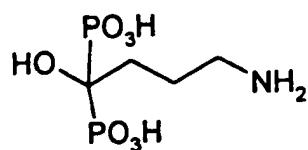
EXAMPLE 4

Preparation of [4-[4-(nitroxy)butyroyl]amino-1-hydroxybutylidene]biphosphonic acid



(E-4)

The precursor drug is alendronic acid of formula



(E-4a)

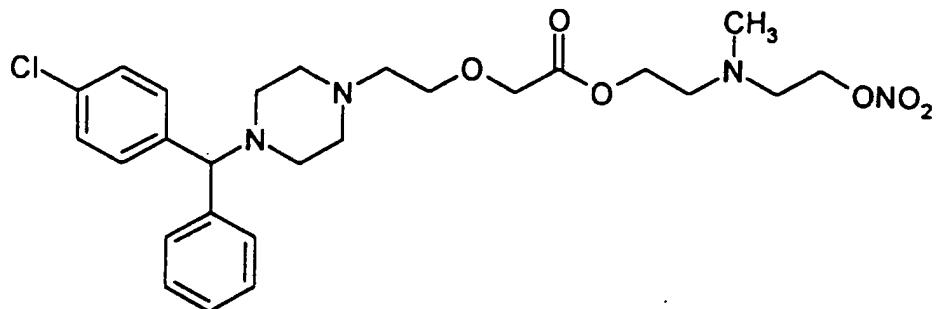
The precursor compound of B is 4-hydroxybutyric acid.

The compound is synthetized according to the procedure described in Example 1. Yield: 11%.

Elementary analysis:	C	H	N
Calculated	25.27%	4.77%	7.37%
Found	25.26%	4.79%	7.37%

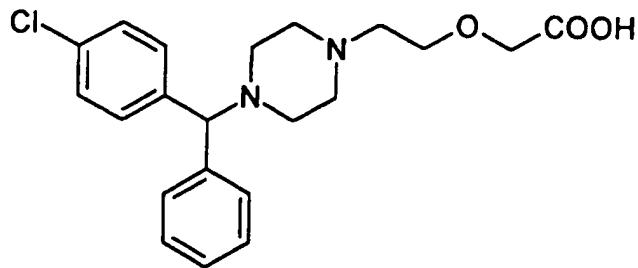
EXAMPLE 5

Preparation of [2-[4-[(4-chlorophenyl)phenylmethyl]1-piperazinyl]ethoxy]acetic acid [N-methyl-N-(2-nitroxyethyl)]-2-aminoethyl ester



(E-5)

The precursor drug is cetirizine



(E-5a)

The precursor compound of B is N-methyldiethanolamine of formula HO-(CH₂)₂-N(CH₃)-(CH₂)₂-OH.

a) Preparation of [2-[4-[(4-chlorophenyl)phenylmethyl]1-piperazinyl]ethoxy]acetic acid [N-methyl-N-(2-hydroxyethyl)]-2-aminoethyl ester

To a solution of cetirizine (5 g, 12.85 mmoles) in N,N-dimethylformamide (5 ml) and toluene (50 ml), cooled at 0°C, oxalyl chloride (1.1 ml, 25.7 mmoles) is slowly added. After

having maintained the reaction mixture under stirring for 12 hours at room temperature, it is evaporated under vacuum. To the obtained crude product, dissolved in tetrahydrofuran (40 ml) N-methyl diethanolamine (4.05 g, 38.55 mmoles) is added and the obtained solution is maintained under stirring at room temperature for 6 hours. The reaction mixture is evaporated at reduced pressure. The residue is treated with ethyl acetate and washed with water. The organic phase is anhydified with sodium sulphate and dried. The crude product is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 3/7 (ratio by volume). [2-[4-[(4-chlorophenyl)-phenylmethyl] 1-piperazinyl]ethoxy]acetic acid [N-methyl-N-(2-hydroxyethyl)]-2-aminoethyl ester is obtained.

b) Preparation of [2-[4-[(4-chlorophenyl)phenylmethyl] 1-piperazinyl]ethoxy]acetic acid [N-methyl-N-(2-chloroethyl)]-2-aminoethyl ester

To a solution of [2-[4-[(4-chlorophenyl)phenylmethyl] 1-piperazinyl]ethoxy]acetic acid [N-methyl-N-(2-hydroxyethyl)]-2-aminoethyl ester (3.8 g, 7.75 mmoles) in chloroform (70 ml), cooled at 0°C, thionyl chloride (0.58 ml, 8.06 mmoles) in chloroform (30 ml) is added. The solution is left at 0°C for 30 minutes under stirring and then heated at 40°C for 6 hours. The reaction is then washed with a saturated sodium bicarbonate solution and subsequently with water. The organic phase, anhydified with sodium sulphate, is evaporated at reduced pressure. The crude product is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 7/3 (ratio by volume). [2-[4-[(4-chlorophenyl)phenylmethyl] 1-piperazinyl]ethoxy]acetic acid [N-methyl-N-(2-chloroethyl)]-2-aminoethyl ester is obtained.

c) Preparation of [2-[4-[(4-chlorophenyl)phenylmethyl] 1-piperazinyl]ethoxy]acetic acid [N-methyl-N-(2-nitroxyethyl)]-2-aminoethyl ester

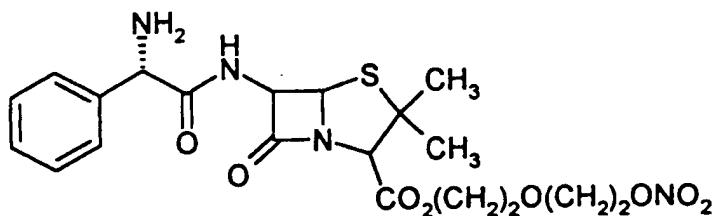
To a solution of [2-[4-[(4-chlorophenyl)phenyl methyl] 1-piperazinyl]ethoxy]acetic acid [N-methyl-N-(2-chloroethyl)]-2-aminoethyl ester (2.3 g, 4.52 mmoles) in acetonitrile (100 ml), silver nitrate (1.53 g, 9.04 mmoles) is added. The reaction mixture is heated to 80°C away from light for 48 hours, then brought again to room temperature, filtered to remove the

silver salts and evaporated at reduced pressure. The residue is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 7/3 (ratio by volume). [2-[4-[(4-chlorophenyl)phenylmethyl]1-piperazinyl]ethoxy]acetic acid [N-methyl-N-(2-nitroxyethyl)]-2-aminoethyl ester is obtained. Yield: 23%.

Elementary analysis:	C	H	N	Cl
Calculated	58.37%	6.59%	10.47%	6.63%
Found	58.38%	6.58%	10.45%	6.60%

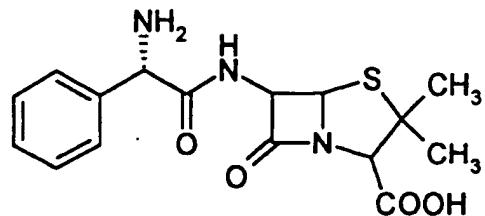
EXAMPLE 6

Preparation of 6-[D(-)-α-aminophenyl acetamido] penicillanic acid 5-(nitroxy)ethyloxethyl ester



(E-6)

The precursor drug is ampicilline of formula



(E-6a)

The precursor compound of B is diethylenglycol.

a) Preparation of 6-[D(-)-α-tert-butoxycarbonylamino phenyl acetamido] penicillanic acid

To a solution of ampicilline (3 g, 8.58 mmoles) in a dioxane (18 ml) and water (25 ml) mixture, triethylamine (2.1 ml, 15.3 mmoles) and di-tert-butyldicarbonate (2.24 g, 10.29 mmoles) are added. The reaction mixture is left under stirring at room temperature for 24 hours, then concentrated at reduced pressure. The residue is treated by subsequent additions of a 1% HCl solution until the pH of the aqueous phase is equal to

7. One extracts with ethyl acetate. The organic phase is anhydified with sodium sulphate and then evaporated under vacuum. 6-[D(-)- α -tert-butoxycarbonylamino phenyl acetamido] penicillanic acid is obtained, which is used in the subsequent synthesis step without further purging.

b) Preparation of 6-[D(-)- α -tert-butoxycarbonylamino phenyl acetamido] penicillanic acid 5-(hydroxy)ethyloxyethyl ester

To a solution of 6-[D(-)- α -tert-butoxycarbonylamino phenyl acetamido] penicillanic acid (3.8 g, 8.58 mmoles) in a mixture of N,N-dimethylformamide (5 ml) and toluene (40 ml), cooled at 0°C, oxalyl chloride (0.74 ml, 17.16 mmoles) is slowly added. The solution is left under stirring for 12 hours at room temperature and then evaporated under vacuum. The obtained crude product is dissolved in tetrahydrofuran (70 ml) and additioned with ethylenglycol (2.45 ml, 25.7 mmoles). The obtained solution is maintained under stirring at room temperature for 5 hours and then evaporated at reduced pressure. The residue is treated with ethyl acetate and washed with water. The organic phase, anhydified with sodium sulphate, is dried. The crude product is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 2/8 (ratio by volume). 6-[D(-)- α -tert-butoxycarbonylamino phenyl acetamido] penicillanic acid 5-(hydroxy)ethyloxyethyl ester is obtained.

c) Preparation of 6-[D(-)- α -tert-butoxycarbonylamino phenyl acetamido] penicillanic acid 5-(chloro)ethyloxyethyl ester

To a solution of 6-[D(-)- α -tert-butoxycarbonylamino phenyl acetamido] penicillanic acid 5-(hydroxy)ethyloxy ethyl ester (3 g, 5.58 mmoles) in chloroform (70 ml), cooled at 0°C, thionyl chloride (0.42 ml, 5.8 mmoles) in chloroform (30 ml) is added. The solution is maintained under stirring at 0°C for 30 minutes and then heated at 40°C for 4 hours. Subsequently the mixture is washed with a saturated sodium bicarbonate solution and then with water. The organic phase is anhydified with sodium sulphate and then evaporated at reduced pressure. The crude product is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 1/1 (ratio by volume). 6-[D(-)- α -tert-butoxycarbonylamino phenyl acetamido] penicillanic acid 5-(chloro)ethyloxyethyl ester is obtained.

d) Preparation of 6-[D(-)- α -tert-butoxycarbonylamino phenyl acetamido] penicillanic acid 5-(nitroxy)ethyloxyethyl ester

To a solution of 6-[D(-)- α -tert-butoxycarbonylamino phenyl acetamido] penicillanic acid 5-(chloro)ethyloxyethyl ester (2.1 g, 3.77 mmoles) in acetonitrile (100 ml), silver nitrate (1.28 g, 7.54 mmoles) is added. The reaction mixture is heated at 80°C for 24 hours away from light. It is cooled at room temperature, filtered to remove the silver salts and evaporated at reduced pressure. The residue is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 1/1 (ratio by volume). 6-[D(-)- α -tert-butoxycarbonylamino phenyl acetamido] penicillanic acid 5-(nitroxy)ethyloxyethyl ester is obtained.

e) Preparation of 6-[D(-)- α -aminophenyl acetamido] penicillanic acid 5-(nitroxy)ethyloxyethyl ester

To a solution of 6-[D(-)- α -tert-butoxycarbonylamino phenyl acetamido] penicillanic acid 5-(nitroxy)ethyloxy ethyl ester (1.5 g, 2.57 mmoles) in ethyl acetate (100 ml), cooled at 0°C, a 5N HCl solution in ethyl acetate (2.67 ml) is added. The solution is maintained at 0°C under stirring for 7 hours and then filtered. The obtained solid is suspended in ethyl acetate and washed with a 5% w/v sodium carbonate solution. The organic phase is washed with water, anhydified with sodium sulphate and evaporated at reduced pressure. The residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 1/1 (ratio by volume). 6-[D(-)- α -amino phenyl acetamido] penicillanic acid 5-(nitroxy)ethyl oxyethyl ester is obtained. Yield: 13%.

Elementary analysis:	C	H	N	S
Calculated	49.79%	5.43%	11.61%	6.64%
Found	49.77%	5.45%	11.60%	6.65%

EXAMPLE 7

Preparation of 2-amino-1,9-dihydro-9-[[2-(4-nitroxybutyroyloxy)ethoxy)methyl]-6H-purin-6-one